REMARKS

The Final Office Action mailed October 18, 2002 and the Advisory Action mailed January 30, 2003 have been received and reviewed. Claims 1-11, 14-19 and 21-23 are pending in the application. All claims stand finally rejected. The Examiner refused entry of applicants' proposed amendments in the amendment filed December 18, 2002 as raising new issues and presenting new claims without canceling a corresponding number of finally rejected claims. Applicants propose to amend claims 6, 11, 15, 16 and 18, add new claims 24 and 25 and cancel claims 17 and 19 as set forth herein. All amendments and cancellations are made without prejudice or disclaimer. Reconsideration is respectfully requested.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 11 and 15-19 stand rejected under 35 U.S.C. § 112, second paragraph, as assertedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Claims 17 and 19 have been cancelled rendering the rejections thereof moot. Partially in view of the proposed amendments, applicants request that the rejections be withdrawn.

Claim 11 was thought to be indefinite for use of the word "interfere." Although applicants do not agree that claim 11 is indefinite, for the sake of expedited prosecution applicants propose to amend claim 11 in accordance with the examiner's suggestion and replace the phrase "interferes with" with the term "inhibits." Reconsideration and withdrawal of the indefinite rejection of claim 11 are, thus, requested.

In the Advisory Action, it was indicated that the indefiniteness rejections of claims 15-19 remained since it was thought that the steps recited by the methods do not necessarily achieve the goal set forth in the preamble. Although applicants do not agree that the claims are indefinite, for the sake of expedited prosecution applicants propose to amend claim 15 to recite in part "identifying the ligand corresponding to the at least one compound that activated said autocrinic loop" to clarify how to determine whether a test compound is a ligand of the orphan receptor in accordance with the suggestion of the Examiner.

In view of the proposed amendments and remarks presented herein, the pending claims should be deemed definite. Accordingly, reconsideration and withdrawal of these rejections are requested.

Rejections under 35 U.S.C. § 103(a)

Claims 1-6, 14 and 21-23

Claims 1-6, 14 and 21-23 stand rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Muthukumaran et al. in view of Trueheart et al. Applicants respectfully traverse the rejections as hereinafter set forth.

A *prima facie* case of obviousness has not been established with regard to independent claim 1 since no suggestion or motivation exists to combine the cited references. For instance, Trueheart et al. is limited to the expression of polypeptides from a library to identify polypeptides that agonize or antagonize receptor bioactivity and does not include a suggestion or motivation to use a chimeric receptor. (*See*, Trueheart et al., page 3). Further, since Muthukumaran et al. is limited to the study of chimeric receptor complexes, no suggestion or motivation exists to use a eukaryotic cell comprising the chimeric receptor in a screening method. (*See*, Muthukumaran et al., page 4993). Thus, no suggestion or motivation exists in the cited references to combine the reference teachings.

"The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." (M.P.E.P. § 2143.01, *quoting In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)). The motivation to combine the cited references provided by the Office states "the benefit of allowing rapid screening of large numbers of compounds that motivates one skilled in the art to combine the teaching of Muthukumaran et al. with the teaching or Trueheart et al. It is unnecessary that the claimed invention be expressly suggested in any one or all of the references to justify combining their teachings; rather, the test is what the combined teachings of the references would have suggested to those or ordinary skill in the art." (Final Office Action, page 4). However, there is no desirability in the cited references to combine them. Thus, the Office is using a

hindsight reconstruction to pick and choose among isolated disclosures in the cited references to assertedly arrive at the claimed invention.

A *prima facie* case of obviousness also cannot be established since one of skill in the art would not have a reasonable expectation of success in combining the teachings of Trueheart et al. with Muthukumaran et al. The Final Office Action indicates that "the chimeric receptor of Muthukumaran et al. might not be functional in yeast cells" indicating that one of skill in the art would not expect the chimeric receptor of Muthukumaran et al. to be functional in the yeast cells of Trueheart et al. (Final Office Action, mailed October 18, 2002, page 4). The Final Office Action also stated "the autocrinic loops in yeast cells taught by Trueheart et al. would assume to work in CHO-B7 and CHO-16-9 cells that express chimeric receptors, as taught by Muthukumaran et al., absence evidence to the contrary. One skilled in the art would be able to combine the autocrinic loops taught by Trueheart et al. with the chimeric receptors in CHO-B7 and CHO-16-9 cells taught by Muthukumaran et al. with a reasonable expectation of success." (*Id.* at page 4).

Applicants respectfully disagree that a reasonable expectation of success as suggested by the Office exists since one of skill in the art would not reasonably expect the autocrinic loops of the yeast cells of Trueheart et al. to be functional in the CHO-B7 and CHO-16-9 cells of Muthukumaran et al. The CHO-B7 and CHO-16-9 cells produce a background (*i.e.*, the hundreds of GPCRs in the CHO cells may produce false positives or constitutively produce signal) that may make screening in the mammalian cells nearly impossible. A review article indicates that mammalian cells include several hundreds of G-protein coupled receptors (GPCRs) while only two GPCRs have been identified in yeast indicating that it is known in the art that background frustrates selection. (*See, e.g.*, Versele et al., *Sex and sugar in yeast: two distinct GPCR systems*, EMBO *reports*, vol. 2, no. 7, 574-579 (2001)) (previously submitted).

It is further known in the art that "one factor which can complicate the use of heterologous expression systems for ligand fishing involves the presence of endogenous receptors in mammalian cell lines and in particular, clonal variation in the pattern of endogenous receptor expression in cells derived from the same parental cell line." (Wilson et al., *Orphan G-protein-coupled receptors: the next generation of drug targets?*, British Journal of

Pharmacology, vol. 125, 1387-1392, at p. 1389 (1998)) (previously submitted). Since yeast cells have a small number of GPCRs, "the ability to genetically delete endogenous GPCRs from yeast to generate a 'null' background is one of the major advantages in using yeast model systems for orphan receptor screening." (*Id.* at 1390). Thus, one of skill in the art would not reasonably expect the autocrinic loops of the yeast cells of Trueheart et al. to work in the mammalian cells of Muthukumaran et al. since the mammalian cells include several hundreds G-protein coupled receptors (GPCRs).

This problem was recognized by Trueheart et al. wherein it is stated that "it will be understood that to achieve selection or screening, the host cell must have an appropriate phenotype. For example, generating a pheromone-responsive chimeric HIS3 gene in a yeast that has a wild-type HIS3 gene would frustrate genetic selection." (Trueheart et al., page 20). Thus, Trueheart et al. recognizes that the wild-type gene would frustrate genetic selection because of the background produced by the wild-type gene and Trueheart et al. teaches away from combining the teachings or Trueheart et al. with Muthukumaran et al. since a "reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." (*Winner International Royalty Corp. v. Ching-Rong Wang*, 202 F.3d 1340, 53 USPQ2d 1580 (Fed. Cir. 2000), *quoting In re Gurley*, 27 F.3d 551, 553, 31 USQP2d 1130, 1131 (Fed. Cir. 1994)).

An additional reason why one skilled in the art would not expect the autocrinic loops of Trueheart et al. to function in the mammalian cells of Muthukumaran et al. is that the responsive CHO cells of Muthukumaran et al. are not normal mammalian cells. The "normal" parental cell line CHO-BH7 of Muthukumaran et al. was not shown to be responsive since the CHO-B7 cells of Muthukumaran et al. transfected with IFNγR2 or γR2/EPOR cDNA showed no response to Hu-INFγ and the "normal" CHO-BH7 cells lack the ligand-binding receptor subunit Hu-IFN-γR1. (*See*, Muthukumaran et al., page 2994). Responsiveness in Muthukumaran et al. was obtained in the specially designed 16-9 hamster x human somatic hybrid cell line which contains a translocation of the long arm of human chromosome 6 and the human HLA-B7 gene. (*Id.* at 2993).

In the Advisory Action, the Examiner indicated "the CHO cells of Muthukumaran et al. are not abnormal, but unique in that transfected chimeric receptors function specifically in response to Hu-IFN-gammaR1 or Epo." (Advisory Action, page 2). The Office is extending the teaching of Muthukumaran et al. too far since the transfected chimeric receptors are disclosed to be expressed in the unique CHO-16-9 cell line and are not expressed in the parental CHO-B-7 cell line. (*See*, Muthukumaran et al., Description of FIGS. 5-7). Thus, the transfected chimeric receptors are only shown to function in the unique CHO-16-9 cell line and not the parental CHO-B-7 cell line.

Accordingly, one of skill in the art could not expect the mammalian cells of Muthukumaran et al. to be a suitable host for the autocrinic loops of Trueheart et al. Without a reasonable expectation of success to combine the cited references, a *prima facie* case of obviousness is not established.

Regarding dependent claims 2-6, 14 and 21-23, they are nonobvious, at the very least, as depending from nonobvious independent claim 1. (*See, In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)).

Accordingly, applicants request reconsideration and withdrawal of the obviousness rejections of independent claim 1, and claims 2-6, 14 and 21-23 depending therefrom.

Claims 7-11

Claims 7, 8 and 10 stand rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Muthukumaran et al. in view of Trueheart et al. as applied above, and further in view of Pellegrini et al.; claim 9 stands rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Muthukumaran et al. in view of Trueheart et al. as applied above, and further in view of Mizushima et al.; and claim 11 stands rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Trueheart et al. in view of Muthukumaran et al. Applicants respectfully traverse the rejections as herein set forth.

Claims 7-11 are nonobvious, at the very least, as directly or indirectly depending from nonobvious independent claim 1. (*See, In re Fine, supra*).

With further regard to claims 7, 8 and 10, they should be considered nonobvious since no suggestion or motivation exists to combine the reference teachings. Pellegrini et al. is limited to a genetic selection method for isolating regulatory mutations in a signaling pathway for alpha interferon and does not suggest or motivate the use of a chimeric receptor, an autocrinic loop or a reporter system. (*See*, Pellegrini et al., Abstract). Further, neither Muthukumaran et al. nor Trueheart et al. suggests or motivates the use of *E. coli* xanthine-guanine phosphoribosyl transferase, a 6-16 reporter or a 2fTGH cell as needed to establish a *prima facie* case of obviousness.

Claim 9 should further be considered nonobvious since Mizushima et al. is limited to the construction of an expression vector using the EF-1α promoter and does not suggest or motivate the use of the EF-1α promoter in combination with the chimeric receptor, the autocrinic or anti-autocrinic loop or the reporter system of claim 1. (*See*, Mizushima et al., page 5322). Also, the Office has not indicated where Muthukumaran et al. or Trueheart et al. suggests or motivates the use of the EF-1α promoter.

Claims 15-19

Claims 15-19 stand rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Trueheart et al. in view of Muthukumaran et al. and claim 19 further stands rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Trueheart et al. in view of Muthukumaran et al. as applied to claims 11 and 15-18 above, and further in view of Watowich et al. Claims 17 and 19 have been cancelled rendering the rejections thereof moot. Applicants respectfully traverse the rejections of claims 15-19 as hereinafter set forth.

Independent claim 15 is nonobvious since a *prima facie* case of obviousness has not been established. As previously set forth herein, no suggestion or motivation exists in Trueheart et al. or Muthukumaran et al. to combine the reference teachings. Further, one of skill in the art would not expect the mammalian cells of Muthukumaran et al. to be a suitable host for the autocrinic loops of Trueheart et al. and without a reasonable expectation of success, there is no obviousness.

Claims 16 and 18 are nonobvious, at the very least, as depending from nonobvious independent claim 15 or 24. (*Id.*).

New claims 24 and 25 should be considered nonobvious since a *prima facie* case of obviousness cannot be established. Since no suggestion or motivation exists to combine Trueheart et al. with Muthukumaran et al. and one of skill in the art would not have a reasonable expectation of success in combining the cited references, new claims 24 and 25 are nonobvious.

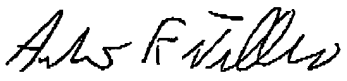
ENTRY OF AMENDMENTS

The proposed amendments to claims 6, 11, 15, 16 and 18 and the addition of new claims 24 and 25 should be entered by the Examiner because the amendments are supported by the as-filed specification and drawings, do not add any new matter to the application and should place the application in condition for allowance. The amendments to claims 11, 15, 16 and 18 should not raise new issues or require a further search since the amendments comply with requirements as to form. Further, the amendments to claims 11 and 15 adopt suggestions of the Examiner. New claims 24 and 25 should be entered because the claims are supported by the as-filed application, should not require a further search and an equal number of claims, *i.e.*, claims 17 and 19, have been cancelled. The elements of new claims 24 and 25 were present in claim 15 and the claims depending therefrom as originally filed. Finally, if the Examiner determines that the amendments do not place the application in condition for allowance, entry is respectfully requested since they certainly remove issues for appeal.

CONCLUSION

In view of the amendments and remarks presented herein, applicants respectfully submit that the amended claims define patentable subject matter. If questions should remain after consideration of the foregoing, the Examiner is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,



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MARKED UP VERSION OF CLAIMS SHOWING CHANGES MADE

6. (Amended) The eukaryotic cell of claim 1 wherein a cytoplasmic part of the chimeric receptor is a cytoplasmic part [of one] of at least one interferon receptor subunit.

11. (Thrice Amended) A method of screening a compound that [interferes with] inhibits the binding of a ligand with the extracellular part of a chimeric receptor and/or with the signaling pathway of the cytoplasmic part of a chimeric receptor, the method comprising:
providing the eukaryotic cell of claim 1;
contacting said eukaryotic cell with said compound; and
selecting cells in which the cell's reporter system is inactivated.

15. (Twice Amended) A method of screening for ligands of an orphan [receptors] receptor [and unknown ligands] comprising:
providing a eukaryotic cell comprising:
a first recombinant gene encoding a chimeric receptor;
a [second recombinant gene] library of recombinant genes encoding [a] at least one compound, the expression of which creates an autocrinic loop;
a reporter system that is activated upon the creation of said autocrinic loop; [and]
selecting cells in which the cell's reporter system is activated[.]; and
identifying the ligand corresponding to the at least one compound that activated said autocrinic loop.

16. (Amended) The method according to claim [15] 24 wherein said series of compounds comprise genes encoding [candidate inhibitors] said antagonists.

18. (Amended) The method according to claim 15 wherein said [unknown] ligands are produced by [an] the autocrinic [or anti-autocrinic] loop.